to. Let's be plain about that. The company is not obligated to make comparisons with other therapies.

Now, the final issue -- or first of all, the basis of dose selection is something that we will definitely be speaking in more detail about this afternoon, and is of course very important.

The final issue is the question of the clinical significance of reducing exogenous insulin therapy and using that as part of the primary efficacy endpoint. In my way of thinking, the approach of the company in their second pivotal study was actually right on. It pretty much mimics sort of the real world approach of clinicians. They are not going to be in a pure sense treating just hemoglobin A1c levels or aiming to improve glycemic control, but they will at the same time be hoping to reduce the amount of exogenous insulin therapy required.

So I think that the categorical

approach taken in their design of the responder analysis, within which we participated, does have some merit, and I hope you will agree.

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Let's just say a few words about efficacy. I really believe there is really no issue here. The treatment effect that was observed in the first pivotal study I think is highly clinically significant. This would translate into a very significant reduction in complications given the DCCT relationship between glycemic control and complications. And it appears to be operating in the way that we would like by working closer to the root of the problem in these patients.

Again, we come back to the responder analysis that was use in the second pivotal study. As I made clear, I believe that this is appropriate, and the results I consider clinically significant.

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(Slide)

Now, let's briefly go over the safety issues. Again, we'll come back to them in the afternoon. First of all, the cardiac effects. Just to summarize, we have seen some toxicity in rodents at high doses. We have the reassurance of no findings in monkeys. However, these were necessarily fairly small studies and at fairly low doses.

We have noticed the increase in blood volume in humans, as was found in animals. I think this could be perhaps related to the cardiac finding, or the effect of increasing animal heart weight. But that remains to be seen.

And of course, we have the monitoring study, where echocardiography is being used to follow the cardiac function of patients that are treated with either Glyburide or troglitazone. And thus far, the results -- well, the results are in, and they are negative. But by thus far I mean I don't

believe that this entirely resolves the issue. Clearly this is not a terribly sensitive way of addressing the issue, though I think it is as good as the company could do at this stage in the drug's development.

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Lipids again we'll come back to this afternoon. And we'll be benefiting from the expertise of Dr. Illingworth, of course, who will be able to make a much better statement about the significance of these changes. It's worth just noting that there are some good things that have been noted. That is, HDL seems to increase, and so do triglycerides.

On the other hand, there is a small but significant increase in serum LDL and, of course, total cholesterol since HDL also increases.

There is also the reference -- and we could call this fluff here because that's just what is being talked about, fluffy LDL

particles that may be somewhat less atherogenic than hard, dense LDL particles. Again, we will await Dr. Illingworth's testimony on this particular point.

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I will bring to your attention the issue of -- well, I'll skip over the change in hematocrit that was observed. I think that is readily explained by the increase in blood volume that was demonstrated both in humans and animals.

But I'll go to an issue that was not really highlighted. Certainly it has been mentioned in the briefing book. And that is that there was in my mind a significant decline in the neutrophil count across all studies. And this amounts to about a 7 percent decline compared with a 1 percent decline in controls.

Now, it is possible this could be related to hemodilution, though I am not aware that there is such an effect in terms of the

white cell series, as you would have the red cells. You could say at least that probably the total neutrophil count does not decrease based on these findings of fluid changes. But again, I think we need to keep in mind that there is an effect on the white cell series. This could have, in the population, some kind of significance, though in the individual certainly this is not clinically significant.

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The other issues that we might talk about a little further this afternoon include our limited experience with long-term exposure.

Now, fortunately, I think we have ample experience. We have much better experience than is exemplified in the -- or is reflected in the briefing book table that deals with this issue. The company does have now, I believe, over 500 patients that exceed the one year in duration of treatment.

We do, I think, have need for more

explanation about how the dose was chosen, and perhaps need for more dose response data. We have one dose response study. I'm not sure that this will be entirely all we would like to have in making some kind of intelligent response about optimization of dosage.

And as I mentioned, we have no knowledge about tissue distribution of the drug in primates. This is maybe to put far down on the wish list. I really hate to see monkeys give their all for this kind of question, which is not going to really definitively answer any of the issues, but might give some reassurance about our concerns related to carcinogenicity and other organ effects.

Well, that is my set of comments about the development and the data that have ensued from the development of this drug. I frankly have been encouraged by the efficacy and the mechanism of action that this drug has shown. Certainly in the introduction of a novel therapeutic approach we have to take sort

of a leap before we -- or we do take a leap in making the drug available without definitive resolution of all of the safety issues.

I feel that the company has done a very good job in addressing these potential safety issues. And I think that we will be benefitting from the advice from the committee in regard to further pursuing them.

This will conclude the FDA presentation, Mr. Chairman.

DR. BONE: Thank you, Dr. Fleming.

Perhaps members of the committee will have questions for either Dr. Steigerwalt or for Dr. Fleming at this point. Anyone? I have one or two.

Dr. Steigerwalt, you referred to the fact that a special committee is reviewing the carcinogenicity issue, particularly I think with respect to the vascular tumors.

Can you tell us the status of that?

DR. STEIGERWALT: We had an initial meeting Monday, I believe, and there were some

questions on the rat study, more for clarification than particular concerns, so that there is going to be another meeting next week. And I was provided with some more information by the sponsor this morning. So we will be --

DR. BONE: But that hasn't been reviewed at this point.

DR. STEIGERWALT: It has been reviewed by the pharmacologist. But it has not be through the carcinogenicity assessment committee.

DR. BONE: I see. So the committee then will, I take it, have to sort of deliberate in the absence of any final information about that particular potential risk.

DR. STEIGERWALT: No. I think we have the amount of information necessary. The committee just has not seen what I saw this morning. And they will be provided with that information, and we should be able to clarify any --

DR. BONE: I mean this committee.

DR. STEIGERWALT: Oh, this committee. That's true.

DR. BONE: Okay. So we will not have the benefit of that information. That remains an open question, I think. All right. Then were there other questions? I have one or two more, but I don't want to -- Dr. Fleming raised the question of the duration of the studies. And particularly since this is a novel class of compounds, we do not have other compounds of this general chemical structure in use.

And obviously, this is a chronic, perhaps perpetual -- perpetual administration is foreseen in millions of people. And for many compounds which will be given for chronic indications in large numbers of people, a somewhat longer, a year or even longer, studies are required for initial approval, I guess both from the standpoint of being certain about the duration of efficacy and also about safety and long term administration.

Dr. Fleming, could you talk about how this decision of six months was arrived at? I think that would be helpful to the committee.

DR. FLEMING: Well, six months is a fairly standard duration for controlled studies, particularly when it involves placebo control. We're often not able to go beyond three to six months in the assessment of an anti-diabetic therapy.

Just as a rule of thumb, we like to have at least 1,000 patient years' exposure and a fair percentage of patients who have been treated in excess of one year. And this is the -- I think the sort of main point about duration is not so much expecting to have controlled trials extending for a one year period, but having to some extent a supplementation with extension of controlled studies, as is the case here.

So we are in the ballpark, I think, for the development of the general indication, that is, the use of troglitazone for the

general population. We have virtually all of the data, safety data, in-house now for that purpose so that we can make a risk/benefit assessment based on this much larger experience.

Obviously, you need far few numbers of patients to address efficacy, and that is why we are satisfied with the relatively small number of patients that were studied in the two pivotal studies. They have amply demonstrated efficacy. Safety requires a much larger end. That end is achieved with the additional data from patients studied under the monotherapy indication being sought.

DR. BONE: Are drug interaction studies being performed in the program with other oral hypoglycemic agents?

DR. FLEMING: Yes. There are data, and that is a very good question because obviously there would be some rationale in using this drug in combination therapy with sulfonylurea agent, obviously.

DR. BONE: Probably we'll get into that this afternoon.

DR. FLEMING: We'll get into that.

DR. BONE: Thank you.

Other questions for either Dr. Steigerwalt or the committee or for other FDA members? Thank you.

Well, it is now 11:50, and I think we should -- excuse me just a second.

(Pause)

DR. BONE: I think we'll have adjournment for lunch, and we'll return at 12:45. All right? We'll start at 12:45 sharp. Thank you.

(Whereupon, at 11:50 a.m., a luncheon recess was taken.)